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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,076	12/31/2003	Sidney N. Wolfe	PP16022.017 (35784/271881	2260

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,076	WOLFE ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Applicants' response to the office action mailed on 10/5/2006, including arguments/remarks and amendments to the claims, was received on 2/5/2007 and has been entered into the record.

2. Claims 1-35 are currently pending and are the subject of this office action.

Claim Objections

Objection to claims 5, 6, 13, 14, 19, 20, 27, 28, 33, and 34, as being of improper dependent form for failing to further limit the subject matter of a previous claim, as set forth on page 2 of the office action mailed on 10/5/2006, is *withdrawn* in response to Applicants' amendments to the claims 5, 13, 19, 27, and 33 to read only on glycosylated interferon (IFN)-β, and Applicants' arguments that claims 6, 14, 20, 28, and 34 are further limiting by reciting IFN-β that is recombinant.

Claim Rejections - 35 USC § 112, first paragraph – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for method of preparing injectable formulations of IFN-β, wherein said IFN-β is a variant or fragment of IFN-β, or is any polypeptide having at least 80% identity to SEQ ID NO: 1, as set forth on pages 3-4 of the office action mailed on 10/5/2006. In the response received on 2/5/2007, the Applicants argue that the specification is enabling because it provides examples of IFN-β variants that were well-known in the art at the time the instant invention was filed, and

that one of ordinary skill in the art would know of assays to determine whether IFN-β variants encompassed by the invention retain biological activity.

These arguments have been fully considered and are not persuasive. As stated in the office action mailed on 10/5/2006, the claims read on a method of preparing formulations of any IFN-β variant or fragment. Although IFN-β variants may be well-known to a skilled artisan, the term "fragment" can encompass virtually any region of amino acids, of any size, from an IFN-β polypeptide. Thus, in light of the specification, the claims can be interpreted as reading on any small "fragment" of an IFN-β polypeptide, wherein said fragment may or may not have biological activity. Furthermore, the claims are also drawn to any polypeptide with at least 80% identity to SEQ ID NO: 1, and are therefore drawn to an excessive number of potential polypeptides because the claims do not require any function for said polypeptides. Although the Applicants point to specific teachings within the specification to identify examples of IFN-β variants, it is not clear which, if any, of the IFN-β polypeptides disclosed in the cited references would be at least 80% identical to SEQ ID NO: 1. If Applicants provide sequence alignments comparing the IFN-b sequences known in the art to SEQ ID NO: 1, and thus show that they are in fact at least 80% identical, then the rejection regarding this limitation will be reconsidered.

The Applicants also argued that the disclosure of Mickle *et al* does not show undue experimentation would be needed to practice the claimed invention because Mickle *et al* teaches a mutation in a cystic fibrosis protein, while the instant application is drawn to much smaller IFN-β polypeptides. The Applicants argue that one of ordinary skill in the art would be able to determine which amino acid residues or regions/domains could be altered and still retain biological activity because IFN-β is a member of a well-characterized protein family. These arguments have been fully considered and are not persuasive. The teachings of Mickle *et al*, as set forth in the previous office action, demonstrate the *unpredictability* inherent in changing the primary amino acid sequence of a protein. Thus, even though IFN-β is a member of a well-characterized family of proteins, one of ordinary skill in the art would also know that one cannot always predict the effects of changing a given amino acid residue(s) in a given protein. Due to this unpredictability that is inherent in the art, and given the excessive breadth of the claims that are drawn to any "fragment" of IFN-β, or any polypeptide, regardless of function, that is at least 80% identical to SEQ ID NO: 1, a person of ordinary skill in the art would require further, undue experimentation in order to determine which of the many possible IFN-β fragments or

polypeptides that are at least 80% identical to SEQ ID NO: 1, would retain any biological activity and thus be useful when prepared by the methods of the claims.

Finally, regarding rejection of claims 4, 12, 18, 26,and 32, drawn to SEQ ID NO: 1 or SEQ ID NO: 2, it is noted that these claims are rejected for depending from rejected base claims.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-35 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of written description formulations of IFN-β, wherein said IFN-β is any variant or fragment of IFN-β, or is any polypeptide having at least 80% identity to SEQ ID NO: 1, as set forth on pages 4-5 of the office action mailed on 10/5/2006. In the response received on 2/5/2007, the Applicants argue that the specification provides examples showing examples of IFN-β variants that were known in the art at the time the instant invention was filed.

This argument has been fully considered and is not persuasive. As set forth above in the enablement rejection, the claims can be interpreted as reading on a methods of preparing any IFN-β variant or fragment. Although the specification provides examples of IFN-β variants that were known in the art at the time the instant invention was filed, there is no description of any IFN-β fragment, or any region from which a fragment could be derived. The claims also are drawn to any polypeptide with at least 80% identity to SEQ ID NO: 1, but do not require any function for said polypeptides. Although the Applicants point to specific teachings within the specification to identify examples of IFN-β variants, it is not clear which, if any, of the IFN-β polypeptides disclosed in the cited references would be at least 80% identical to SEQ ID NO: 1. However, if Applicants can show that the references cited in the specification do in fact disclose IFN-b polypeptides having at least 80% identity to SEQ ID NO: 1, then this rejection will be reconsidered.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claims 7, 15, 21, 29, and 35 under 35 USC § 112, second paragraph, as being indefinite regarding IFN-β polypeptides having at least 80% identity to SEQ ID NO: 1 as calculated using the ALIGN program, as set forth on page 5 of the prior office action mailed on 10/5/2005, is *withdrawn* in response to Applicants' amendments to the claims to specifically recite version 2.0 of the ALIGN program.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 8-35 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Arora *et al* ("Arora") and Dorin *et al* ("Dorin"), as set forth on pages 6-7 of the office action mailed on 10/5/2006. The claims of the instant invention are drawn to methods of preparing an injectable formulation of IFN-β, wherein said methods comprise denaturing IFN-β by dissolving said IFN-β in guanidine hydrochloride followed by renaturation of IFN-β by dilution into a buffer. In some cases, the claims are also drawn to methods comprising removal of guanidine by diafiltration or dialysis into a second buffer. The claims also recite buffers of various pH and guanidine concentrations, and IFN-β that is glycosylated or unglycosylated, produced recombinantly, or represented by the amino acid sequences set forth in SEQ ID NOs 1 or 2.

Arora *et al* teaches methods of preparing properly folded recombinant IFN-γ. Specifically, Arora *et al* discloses a method whereby IFN-γ present in E. coli inclusion bodies is dissolved in guanidine hydrochloride, followed by renaturation of the dissolved IFN-γ by dilution in refolding buffer at pH 8.0, with or without arginine. The renatured IFN-γ was then dialyzed against a second buffer at pH 8.0 (see p. 130, paragraphs 3.5-3.7). Arora *et al* is silent regarding guanidine hydrochloride concentrations after dilution or dialysis, a first buffer with a pH between 3.0 and 5.0, or purification of any IFN-β polypeptide.

Dorin *et al* discloses a polypeptide sequence (SEQ ID NO: 1 of Dorin *et al*) with 100% identity to SEQ ID NO: 1 of the instant application (see sequence comparison 1), and teaches

that IFN-β is useful for treatment of diseases such as multiple sclerosis and hepatitis b or c (column 1, lines 14-20).

In the response received on 2/5/2007, the Applicants argue the teachings of Arora and Dorin would not motivate a skilled artisan to arrive at the claimed methods of preparing IFN-β because Arora discloses methods of isolating IFN-γ, and not IFN-β. The Applicants further argue that one of ordinary skill in the art would know that multiple factors affect isolation and purification of recombinant proteins, each dependent upon the nature of the protein itself (see Fiona *et al* - submitted as Exhibit A). Therefore, the Applicants argue that there is no motivation to combine the teachings of Arora and Dorin, and these teachings are, at best an invitation to perform additional experiments. Furthermore, the Applicants assert that any combination of these references is based on hindsight reconstruction.

These arguments have been fully considered and are not persuasive. In response to the Applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the teachings of Arora highlight the fact that protein isolation using guanidine HCL was known in the art at the time the instant invention was filed, while Dorin shows that the protein of SEQ ID NO: 1 was also known at the time the instant invention was filed, and was known to be a protein that is useful for treatment of a number of diseases. Thus, one of ordinary skill in the art would know of a method of protein purification that promotes proper protein refolding (see Arora, p. 131, section 4.1), and would therefore be motivated to use this method to purify the therapeutically useful protein of Dorin. Furthermore, although neither Arora nor Dorin teach buffers in the claimed pH range, and specific concentrations of guanidine HCL, the Applicants assert that "multiple factors affect isolation and purification of recombinant proteins, each dependent upon the nature of the protein itself". Thus a skilled artisan, knowing that each individual protein may in fact require specific conditions, would be both motivated, and able, to optimize conditions such as pH and guanidine HCL concentration in order to practice the claimed method. For these reasons, the combination of Arora and Dorin provides a person of ordinary skill in the art with the motivation, and a

reasonable expectation of success, in practicing the claimed methods of IFN-β formulation.

2. Claims 1-7 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of van Oss, Arora *et al* ("Arora"), and Dorin *et al* ("Dorin"), as set forth on pages 7-8 of the office action mailed on 10/5/2006. The subject matter of the claims of the instant invention, as well as the teachings of Arora and Dorin, are discussed supra. Claims 1-7 are drawn to a method of preparing an injectable formulation of IFN-β, wherein said method comprises a first step of precipitating IFN-β using an alcohol, followed by purification as described in the preceding rejection. van Oss teaches that ethanol precipitation of proteins is well-known in the art and is a common and accepted method of protein isolation (p. 661, 1st paragraph).

The Applicants arguments regarding the teachings of Arora and Dorin are described supra. In the response received on 2/5/2007, the Applicants further argue that the disclosure of van Oss does not further remedy the deficiencies of the Arora and Dorin references, because this combination teaches purification of IFN-γ, and thus nothing in this combination of references provides the motivation to practice the claimed method of preparing a formulation of IFN-β.

These arguments have been fully considered and are not persuasive. As stated in the previous rejection, the combination of Arora and Dorin provide the motivation, and a reasonable expectation of success, in practicing methods of preparing IFN-β formulations. The disclosure of van Oss, by teaching that ethanol precipitation of proteins is a method of protein isolation/purification that is well-known in the art, provides the motivation to precipitate IFN-β using an alcohol such as ethanol. Thus, the combination of Arora, Dorin, and van Oss disclose information that would have been known to a person of ordinary skill in the art at the time the claimed invention was made, and therefore claims 1-7 of the instant invention are obvious in view of this combination of references.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER